201-14643

NCIC HPV
Sent by: Mary-Beth Weaver

08/05/2003 12:24 PM

To: NCIC HPV, moran.matthew@epa.gov
cc:
cc:
Subject: Response to EPA Comments - GE Plastics CAS RNs 550-44-7, 41663-84-7, 527-60-6

"John P. Van Miller" <jvanmiller@toxregserv.com> on 08/05/2003 10:49:18 AM

To: oppt.ncic@epamail.epa.gov, Rtk Chem/DC/USEPA/US@EPA
cc: "Ronald L Joiner (GEP)" <Ronald.Joiner@gepex.ge.com>, Stephen Dimond <stephen.dimond@gep.ge.com>

Subject: Response to EPA Comments - GE Plastics CAS RNs 550-44-7, 41663-84-7, 527-60-6

Attached please find responses to EPA's comments on the following Test Plans for the HPV Chemical Challenge Program:

1) N-Methylphthalimide (PI: CAS RN 550-44-7)
2) 4-Nitro-N-Methylphthalimide (4-NPI: CAS RN 41663-84-7)
3) 2,4,6-Trimethylphenol (246-TMP: CAS RN 527-60-6)

Thank you.

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PI_CAS 550-44-7_GE Response_August 5 2003.pdf

4-NPI_CAS 41663-84-7_GE Response_August 5 2003.pdf

246-TMP_CAS 527-60-6_GE Response_August 5 2003.pdf

TRS
TOXICOLOGY/REGULATORY SERVICES, INC.

August 5, 2003

Linda Fisher, Acting Administrator
US Environmental Protection Agency
PO Box 1473
Merrifield, VA 22116

Attention: Chemical Right-to-Know Program, AR-201

Via Electronic Submission

Re: Response to Comments on Test Plan for CAS RN 41663-84-7

On behalf of General Electric Company – Plastics (GE Plastics; Registration Number 1100342), Toxicology/Regulatory Services (TRS) is submitting responses to the EPA Comments on Test Plans/Robust Summaries for 4-Nitro-N-Methylphthalimide (CAS RN 41663-84-7). Please address any further correspondence to:

Dr. Ronald L. Joiner
Manager, Global Toxicology
General Electric Company
One Plastics Avenue
Pittsfield, MA 01201
Phone: 413-448-6323; Fax: 413-448-6590
EMAIL: Ronald.Joiner@GEP.GE.COM

Thank you,

John P. Van Miller, Ph.D., DABT

General Electric Company – Plastics: Response to Comments on the Test Plan for 4-Nitro-N-Methylphthalimide (CAS RN 41663-84-7)

Below is a reproduction of the comments submitted to the General Electric Company – Plastics (GE Plastics) Test Plan submission for the above referenced chemical in the HPV Challenge Program. Questions and comments from EPA that require input are formatted in ***Bold/Italic*** font and GE Plastic's response follows each entry. Responses are made to specific comments rather than Summary Comments.

EPA Comments on Chemical RTK HPV Challenge Submission: 4-Nitro-N-Methylphthalimide

Summary of EPA Comments

The sponsor, General Electric Company-Plastics (GE Plastics), submitted a test plan and robust summaries to EPA for 4-Nitro-N-Methylphthalimide (4-NPI) (CAS No. 41663-84-7) dated December 30, 2002. EPA posted the submission on the ChemRTK HPV Challenge Web site on January 30, 2003.

EPA has reviewed this submission and has reached the following conclusions:

1. Physicochemical Properties. The data provided by the submitter for melting point, boiling point, partition coefficient, and water solubility are adequate for the purposes of the HPV Challenge Program. EPA agrees with the submitter's proposal to determine vapor pressure.

2. Environmental Fate. The data provided by the submitter for stability in water (hydrolysis) are adequate for the purposes of the HPV Challenge Program. EPA agrees with the submitter's test plan for photodegradation, transport and distribution, and biodegradation.

3. Health Effects. The submitter proposed testing for the reproduction toxicity endpoint. Because there is an adequate developmental toxicity study, EPA believes that the reproduction toxicity endpoint may be addressed if the submitter provides information on histopathologic evaluation of the reproductive organs for both sexes from the submitted 13-week repeated-dose oral toxicity test.

4. Ecological Effects. The studies for fish, invertebrates, and algae endpoints are inadequate. Testing is needed to address these endpoints.

EPA requests that the submitter advise the Agency within 60 days of any modifications to its submission.

EPA Comments on the 4-nitro-n-methylphthalimide Challenge Submission

General

EPA has evaluated this submission as if the chemical were not used as a closed system intermediate. However, the use pattern described in the submission "...a site-limited intermediate made at a single location in the U.S....used as a reactive intermediate to make high molecular weight polyetherimide polymer" indicates that the submitter may have the option to submit as a site limited intermediate if supporting information is provided. The Guidance for Testing Closed System Intermediates for the Challenge Program allows for a reduced testing protocol provided certain criteria are met (refer to http://www:epa.gov/chemrtk/closed9.htm).

RESPONSE: Please note that the quotation cited above actually reads "… **primarily** a site-limited …" [emphasis supplied]. The approach to all reporting/testing programs is designed to be consistent with GE's global business goals rather than to respond within a specific regulatory framework. The global use of 4-NPI is not exclusively as a site-limited intermediate nor will it necessarily remain a low volume sales product. Therefore, 4-NPI was not declared a site-limited intermediate for the HPV Challenge Program.

Test Plan

Physicochemical Properties (melting point, boiling point, vapor pressure, partition coefficient and water solubility).

The data provided by the submitter for melting point, boiling point, partition coefficient, and water solubility are adequate for the purposes of the HPV Challenge Program. There are some discrepancies in the test plan and in the robust summaries regarding partition coefficient and water solubility that need to be corrected.

RESPONSE: Discrepancies will be corrected in the final submission.

Vapor pressure. The submitter indicates in the test plan that testing is needed for the vapor pressure endpoint. EPA agrees. To satisfy this endpoint, the submitter needs to provide vapor pressure data following OECD TG 104.

RESPONSE: The appropriate test or Expert Statement will be provided in the final submission.

Partition coefficient and water solubility. In the test plan (page 4) the submitter states that GLP-compliant OECD methods were used to determine the logKow and water solubility for 4-NPI; however, in the robust summaries the submitter states that measurements using OECD TGs 105 and 107 were not possible due to significant hydrolysis of 4-NPI during the course of testing. The submitter provided a calculated logKow and water solubility for 4-NPI. The test plan (page 4) needs to be modified to reflect the data in the robust summaries for these endpoints.

RESPONSE: The Test Plan table on page 4 will be changed to reflect that the values were calculated because the OECD Guideline studies could not be conducted.

Environmental Fate (photodegradation, stability in water, biodegradation, fugacity).

Adequate data are available for stability in water (hydrolysis) for the purposes of the HPV Challenge Program. The submitter indicates in the test plan that testing is needed for the photodegradation, transport and distribution, and biodegradation endpoints. EPA agrees with the test plan for these endpoints.

RESPONSE: Photodegradation and transport and distribution will be provided in the final submission using an Expert Statement for the EPIWIN model consistent with the EPA's guidance for these endpoints in the HPV Challenge Program.

Biodegradation. To address the biodegradation endpoint, the submitter needs to provide measured ready biodegradation data following OECD TG 301. Considering that this chemical undergoes rapid hydrolysis, the submitter needs to provide biodegradation data on the hydrolyzed product.

RESPONSE: The biodegradation study will be conducted using OECD 301B on the hydrolysis products.

Health Effects (acute toxicity, repeated-dose toxicity, genetic toxicity, and reproductive/developmental toxicity).

Adequate data are available for the acute, repeated-dose, genetic, and developmental toxicity endpoints for the purposes of the HPV Challenge Program.

Reproduction Toxicity. No data were submitted. The submitter proposed testing for this endpoint; however, this testing may not be needed if the submitter provides information on histopathologic evaluation of the reproductive organs for both sexes from the submitted 13-week repeated-dose oral toxicity test. Such information along with the adequate developmental toxicity study will address the reproduction toxicity endpoint for the purposes of the HPV Challenge Program. If testing is needed, the submitter should use OECD TG 421 (combined reproductive/devlopmental screening test).

As noted above, the approach to all reporting/testing programs is designed to be consistent with GE's global business goals rather than to respond within a specific regulatory framework. Therefore, 4-NPI was not declared to be a site-limited intermediate and it is consistent with GE's needs to fulfill the screening dataset for reproduction with a study conducted in compliance with OECD 421. This study is being conducted via oral gavage dosing.

Ecological Effects (fish, invertebrates, and algae).

The submitted studies for fish, invertebrates, and algae are inadequate because the maximum nominal concentrations tested (15.06 mg/L) were well below the water solubilities for the sponsored substance (360 mg/L) or its hydrolysis product (1000 mg/L). Since the half life of 4-NPI is 6.4 hours at pH 7, EPA suggests the testing be conducted on the hydrolyzed product (4-NPI-H) on all three species using mean measured concentrations.

RESPONSE: The following paragraph from the Robust Summary defines the toxicity of 4-NPI to aquatic plants (algae):

"… the 72- and 96-hour EC50s for cell number were 5.54 and 10.52 mg/L, respectively. The 72- and 96-hour EC50s for area under the growth curve were 5.36 and 7.80 mg/L,

respectively. The 0 to 72 and 0 to 96-hour EC50s for growth rate were > 15.06 mg/L, the highest concentration of active ingredient tested. For four endpoints (72-hour cell number, 72- and 96-hour area under the growth curve and 72 hour growth rate), the NOECs were 1.44 mg/L and the LOECs were 2.58 mg/L. For 96-hour cell number, the NOEC and LOEC were 2.58 and 4.65 mg/L, respectively. For 96-hour growth rate, the NOEC and LOEC were 4.65 and 8.37 mg/L, respectively."

RESPONSE: LOECs and an EC_{50} for area under the curve were established for algae in this study. Because risk assessment uses the lowest concentration causing effects in any of the three acute screening studies for aquatic toxicity, these values would be employed. Therefore, there is no regulatory purpose in conducting aquatic toxicity studies with fish or *Daphnia* at higher concentrations than the 15.06 mg/L already tested. That is, refined EC_{50} values above 15.06 mg/L would not be used for risk assessment purposes.

Specific Comments on the Robust Summaries

Health Effects.

Repeated-Dose Toxicity. The submitter needs to provide histopathological data of the reproductive organs, if available, for the robust summary of the submitted 13-week gavage study in rats.

RESPONSE: The approach to all reporting/testing programs is designed to be consistent with GE's global business goals rather than to respond only within a specific regulatory framework. Therefore, it is consistent with GE's global needs to fulfill the screening dataset for reproduction with a study conducted in compliance with OECD 421. This study is being conducted via oral gavage dosing and is scheduled for completion in calendar year 2003.

Followup Activity

EPA requests that the submitter advise the Agency within 60 days of any modifications to its submission.